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RESEARCH ARTICLE

Structure and bioactivity of triterpenoids from the stems of *Schisandra sphenanthera*

Cheng-Qin Liang · Rong-Hua Luo · Ju-Ming Yan · Yan Li · Xiao-Nian Li · Yi-Ming Shi · Shan-Zhai Shang · Zhong-Hua Gao · Liu-Meng Yang · Yong-Tang Zheng · Wei-Lie Xiao · Hong-Bin Zhang · Han-Dong Sun

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Abstract Two new triterpenoids, schisphendilactone A and B (**1** and **2**), together with three known triterpenoids, were isolated from the stems of *Schisandra sphenanthera*. Their structures were elucidated by spectroscopic methods, and the absolute configuration of **1** was determined by single-crystal X-ray diffraction. Compound **2** showed moderate inhibitory activity against SW480 cancer cell line, and compound **5** exhibited promising anti-HIV-1 activity with EC_{50} value of 0.52 μg ml^{-1} and therapeutic index value of 117.12.

C.-Q. Liang · J.-M. Yan · Y. Li · X.-N. Li · Y.-M. Shi · S.-Z. Shang · Z.-H. Gao · W.-L. Xiao (✉) · H.-D. Sun (✉)
State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, Yunnan, People's Republic of China
e-mail: xwl@mail.kib.ac.cn

H.-D. Sun
e-mail: hdsun@mail.kib.ac.cn

C.-Q. Liang · H.-B. Zhang
Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, Yunnan, People's Republic of China

C.-Q. Liang · Y.-M. Shi · S.-Z. Shang · Z.-H. Gao
University of Chinese Academy of Sciences, Beijing 100039, People's Republic of China

R.-H. Luo · L.-M. Yang · Y.-T. Zheng
Key Laboratory of Animal Models and Human Disease Mechanisms of Chinese Academy of Sciences & Yunnan Province, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, Yunnan, People's Republic of China

Keywords *Schisandra sphenanthera* · Triterpenoid · Cytotoxicity · Anti-HIV-1

Introduction

The genus *Schisandra* (Schisandraceae family) have been proven to be a rich source of lignans and nortriterpenoids, some of which were reported to have antihepatitis (Kuo et al. 2001), antiviral (Chen et al. 2002), antifeedant (Chang et al. 2005), and anti-HIV (Chen et al. 1996; Li et al. 2005; Xiao et al. 2005a, b) activities. *Schisandra sphenanthera* Rehd. et Wils is a kind of liana mainly distributed in the southern and middle region of China (Gu et al. 2008). Previous chemical studies on this plant collected from Sichun province of China led to the isolation of several nortriterpenoids, including schinalactones A–C, pre-schisanartanins E–J and sphenadilactones D–F and some of them showed cytotoxic activity (He et al. 2010, 2012). Aiming at searching for more biologically active triterpenoids, we have investigated the stems of *S. sphenanthera*, collected in Qinling region of Shanxi province of China. As a result, Two new triterpenoid lactones, schisphendilactones A and B (**1** and **2**), together with nigranoic acid (**3**) (Sun et al. 1996), kadsuric acid (**4**) (Yamada et al. 1976), lancifoic acid A (**5**) (Xiao et al. 2006) were isolated. This paper deals with the isolation and structural elucidation of the isolated triterpene constituents, as well as their cytotoxic and anti-HIV-1 activities.

Materials and methods

General experimental procedures

Melting point was obtained on an XRC-1 apparatus and was uncorrected. Optical rotations were measured with a

JASCO DIP-370 digital polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A BioRad FtS-135 spectrophotometer was used for scanning IR spectroscopy with KBr pellets, whereas CD spectra were recorded on a JASCO J-810 spectropolarimeter. 1D and 2D NMR spectra were recorded on Bruker AM-400 spectrometers. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. EIMS were recorded on Waters AutoSpec Premier P776 spectrometer at 70 eV. ESIMS were performed on a Xevo TQ-S mass spectrometer, HRESIMS were performed on an API QSTAR time-of flight spectrometer. X-ray data were collected using a Bruker APEX DUO instrument. Silica gel (100–200 mesh, Qingdao Marine Chemical, Inc., Qingdao, People's Republic of China), Lichroprep RP-18 gel (40–63 μM, Merck, Darmstadt, Germany), Sephadex LH-20 (Pharmacia), and MCI gel (75–150 μM, Mitsubishi Chemical Corporation, Tokyo, Japan) were used for Column chromatography. Semipreparative HPLC was performed on an Agilent 1100 or 1200 liquid chromatography with a Zorbax SB-C_{18} (5 μM, 9.4 mm × 25 cm) column. Fractions were monitored by TLC and spots were visualized by heating the silica gel plates sprayed with 10 % H_2SO_4 in EtOH.

Plant material

The stems of *S. sphenanthera* were collected in Qinling Country of Shanxi Province, People's Republic of China, in December 2008, and identified by Professor. Xi-Wen Li, Kunming Institute of Botany. A voucher specimen (KIB 2008121006) has been deposited in the Herbarium of the Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and isolation

The air-dried and fine powdered stems (19.5 kg) of *S. sphenanthera* were extracted with the 70 % aqueous acetone (100 L × 3, each 3 day) at room temperature. After filtration, the solvent was concentrated under vacuum and partitioned between EtOAc and H_2O. The EtOAc soluble portion (1.0 kg) was chromatographed by using silica gel (100–200 mesh, 3.0 kg) column, eluting with a $CHCl_3$–Me_2CO gradient system (1:0, 9:1, 8:2, 2:1, 1:1, 0:1), to give seven fractions A–G. fraction C (33 g) was decolorized on MCI gel column (7 × 60 cm, eluent MeOH–H_2O, 9:1; 2,000 ml), and after concentration, it was subjected to RP-18 column chromatography (30–100 % gradient MeOH–H_2O) to afford five subfractions, fractions CI–CV. Fraction CII (1.35 g) was purified by semipreparative HPLC (70 % CH_3CN–H_2O; 3 ml min^{-1}; UV detector, 210 nm) to give **3** (10.0 mg), **4** (7.5 mg) and **5** (6.3 mg). Fraction CIV (4.3 g) was purification on Sephadex LH-20 column chromatography and then semipreparative HPLC repeatedly (eluted with 50 % CH_3CN–H_2O; 3 ml min^{-1}; UV detector, 210 nm) to afford **1** (12.5 mg) and **2** (10.4 mg).

Schisphendilactone A (**1**)

Colorless crystals in MeOH. m.p.: 121–122 °C; $[\alpha]_D^{15}$ = +114.7 (*c* 0.47, $CHCl_3$); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 238 (−7.6); UV ($CHCl_3$) λ_{max} (log ε) 248 (3.42) nm; IR (KBr) ν_{max} 3443, 2971, 2925, 1715, 1683, 1389, 1377, 1119 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Table 1; EIMS *m/z* 482 ($[M]^+$), 464, 302, 173,147, 111, 95; ESIMS *m/z* (100, 505 $[M + Na]^+$); positive HRESIMS *m/z* 505.2919 (calcd for $C_{30}H_{42}O$ 5Na, 505.2929).

Schisphendilactone B (**2**)

White powder; $[\alpha]_D^{14} = -42.1$ (*c* 0.22, MeOH); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 257 (–11.3); UV (MeOH) λ_{max} (log ε) 221 (4.58), 201 (4.33) nm; IR (KBr) ν_{max} 3434, 2960, 1714, 1662, 1391, 1378, 1131, 1118 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Table 1; EIMS *m/z* 494 ($[M]^+$), 466, 279, 167,149, 111, 55; ESIMS *m/z* 517 (100, $[M + Na]^+$); negative HRESIMS *m/z* 493.2588 (calcd for $C_{30}H_{37}O_6$, 493.2590).

X-ray crystal structure analysis of **1**

$C_{60}H_{84}O_{10}$ (2 × $C_{30}H_{42}O_5$, M_W = 965.3), monoclinic, space group, $P2_1$, Z = 2, a = 8.0353(2) Å, b = 32.2688(9) Å, c = 10.6842(3) Å, $\alpha = \gamma = 90°$, β = 112.0480(10)°, V = 2567.71(12) $Å^3$. μ(Cu Kα) = 0.661 mm^{-1}, D_{calc} = 1.248 g cm^{-3}; S = 1.067, final R_1 = 0.0414, wR_2 = 0.1133 for 8,320 observed from 8,372 independent and 20,864 measured reflections, (θ_{max} = 69.43, $I > 2\sigma$ (I) criterion and 645 parameters); maximum and minimum residues are 0.262 and −0.295 e $Å^{-3}$, respectively. The Flack parameter value was x = 0.14(11), indicating that the absolute structure has been determined correctly (Flack 1983) *Crystallographic* data of **1** have been deposited in the *Cambridge Crystallographic Data Center* (no. CCDC 896064). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB 1EZ, UK [fax: Int. +44 (0) (1223) 336 033); e-mail: deposit@ccdc.cam.ac.uk].

Cytotoxicity assay

The following human tumor cell lines were used: HL-60 (human myeloid leukemia cell line), SMMC-7721 (human

Table 1 ^{1}H- and ^{13}C-NMR data of compounds **1** and **2** (in $CDCl_3$)

No.	**1**		**2**	
	δ_H (mult., *J* in Hz)[a]	δ_C[b]	δ_H (mult., *J* in Hz)[a]	δ_C[b]
1	6.12 (d, 12.6)	149.8	5.73 (d, 12.5)	142.8
2	5.92 (d, 12.6)	120.5	6.22 (d, 12.5)	127.5
3		167.2		165.4
4		84.2		81.3
5	2.45 (dd, 13.9, 4.3)	44.4	1.61 (m)	49.9
6a	0.96 (overlap)	33.2	1.98 (m)	22.3
6b	2.04 (overlap)		1.98 (m)	
7a	3.66 (m)	68.5	2.38 (overlap)	27.1
7b			2.52 (m)	
8	1.95 (d, 6.0)	51.2		165.4
9		29.0		128.6
10		33.5		58.1
11a	1.34 (overlap)	29.0		197.5
11b	1.81 (m)			
12	1.58 (overlap)	31.9	2.64 (s)	48.7
13		45.6		51.7
14		48.3		47.6
15a	1.42 (overlap)	34.7	1.54 (overlap)	30.8
15b	1.58 (overlap)		1.83 (overlap)	
16a	1.41 (overlap)	26.8	1.56 (overlap)	25.7
16b	1.76 (overlap)		1.92 (overlap)	
17	1.54 (m)	47.2	1.82 (overlap)	45.8
18	0.96 (s)	15.9	0.94 (s)	17.0
19a	0.89 (d, 5.6),	28.2	3.70 (s)	58.4
19b	1.42 (overlap)			
20	1.99 (overlap)	39.1	2.07 (overlap)	39.2
21	0.94 (d, 6.3)	13.3	1.00 (d, 6.6)	13.5
22	4.43 (m)	80.4	4.44 (m)	79.8
23a	2.08 (overlap)	23.4	2.40 (overlap)	23.6
23b	2.34 (m)		2.09 (overlap)	
24	6.59 (d, 6.5)	139.5	6.60 (d, 6.2)	138.9
25		128.1		128.6
26		166.6		166.2
27	1.87 (s)	16.9	1.91 (s)	17.0
28	0.82 (s)	18.6	1.12 (s)	24.7
29	1.34 (s)	21.5	1.67 (s)	24.6
30	1.35 (s)	29.4	1.40 (s)	28.7

[a] Recorded at 400 MHz

[b] Recorded at 100 MHz

hepatocarcinoma cell line), A-549 (lung cancer cell line), MCF-7 (breast cancer cell line) and SW480 (human colon carcinoma). All the cells were cultured in RPMI-1640 or DMEM medium (Hyclone, Logan, UT), supplemented with 10 % fetal bovine serum (Hyclone, USA) at 37 °C in a humidified atmosphere with 5 % CO_2. Cell viability was assessed by conducting colorimetric measurements of the amount of insoluble formazan formed in living cells based on the reduction of *3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide* (MTT) (Sigma, St. Louis, MO). Briefly, 100 µl adherent cells were seeded into each well of a 96-well cell culture plate and allowed to adhere for 12 h before drug addition, while suspended cells were seeded just before drug addition, both with initial density of 1×10^5 cells ml^{-1} in 100 µl medium. Each tumor cell line was exposed to the tested compound at various concentrations in triplicates for 48 h, with *cis*platin (Sigma, USA) as positive control. After the incubation, MTT (100 µg) was added to each well, and the incubation continued for 4 h at 37 °C. The cells were lysed with 100 µl 20 % SDS-50 % DMF after removal of 100 µl medium. The optical density of the lysate was measured at 595 nm in a 96-well microtiter plate reader (Bio-Rad 680, USA). The IC_{50} value of each compound was calculated by the Reed and Muench's method (Monks et al. 1991).

Anti-HIV-1 assay

The cytotoxicity assay against C8166 cells (CC_{50}) was assessed by using the MTT method, and the anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50}) (Wang et al. 2009).

Results and discussion

Schisphendilactone A (**1**) was obtained as colorless crystals. The positive HRESIMS showed a quasi-molecular ion peak at *m/z* 505.2919 ($[M + Na]^+$, calcd 505.2929), which in accordance with NMR data enabled the molecular formula $C_{30}H_{42}O_5$, accounting for ten degrees of unsaturation. The UV spectrum showed λ_{max} at 248 nm. The IR spectrum suggested the presence of hydroxyl (3,443 cm^{-1}) and α,β-unsaturated lactone carbonyl (1,715 and 1,683 cm^{-1}) groups in the structure. The ^{1}H NMR spectrum (Table 1) revealed five three-proton singlets at δ_H 1.87, 1.35, 1.34, 0.96 and 0.82, one three-proton doublet at δ_H 0.94 (d, $J = 6.3$ Hz). Additionally, two signals attributed to two oxymethine protons were observed as multiplets at δ_H 4.43 and 3.66. The ^{13}C NMR spectrum (Table 1) displayed signals for 30 carbon atoms which were assigned by DEPT and HSQC spectra to nine low-field signals corresponded to two carbonyl (δ_C 166.6 and 167.2), four olefinic (δ_C 120.5, 128.1, 139.5, and 149.8) and three oxygenated carbons (δ_C 68.5, 80.4, and 84.2), and high-field signals were assigned to six methyl, seven methylene, four methine and five quaternary carbons. These spectroscopic data closely resembled those of kadsulactone A (Chen et al. 1990). Compound **1** and kadsulactone A both had a six-membered

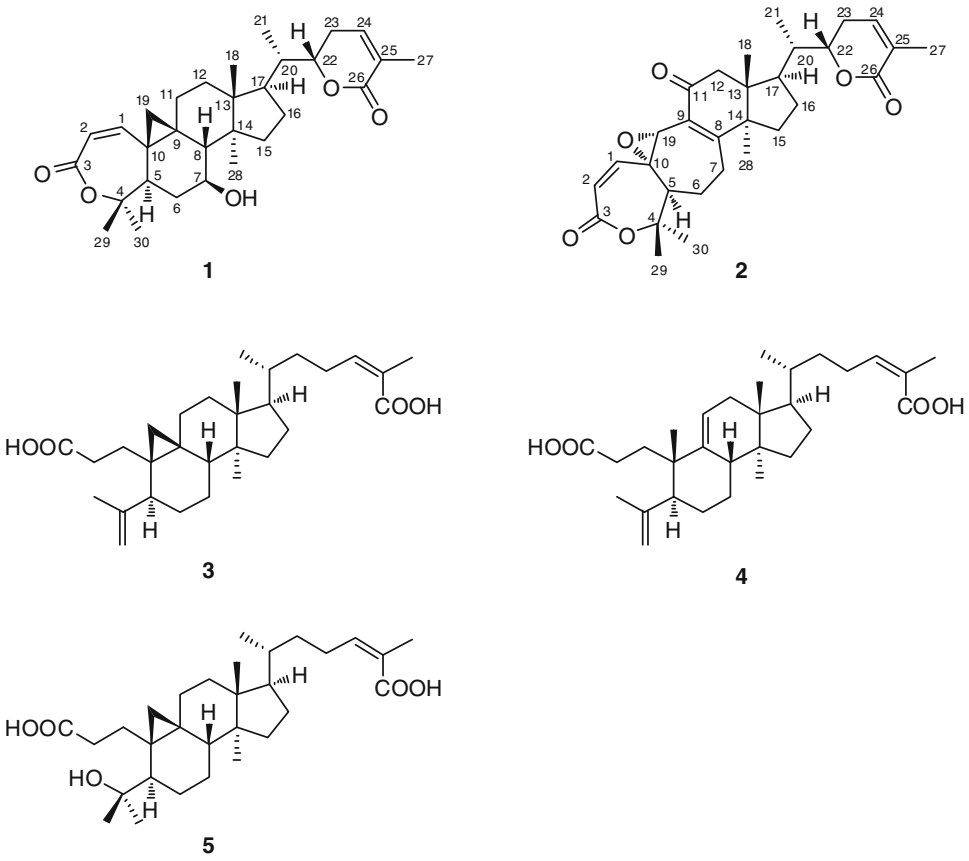

Fig. 1 Structures of compounds **1**–**5**

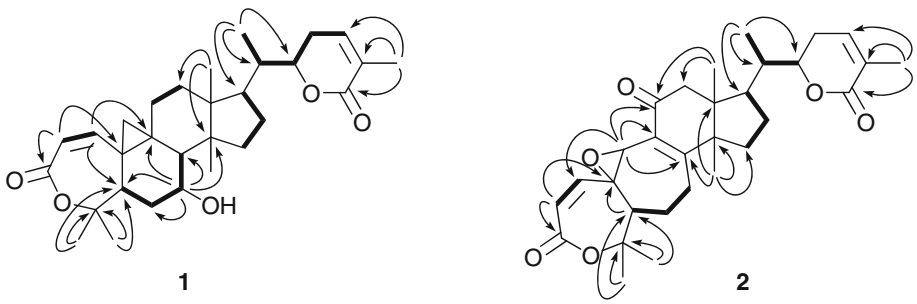

Fig. 2 Selected ^{1}H–^{1}H COSY(H ▬ H) and HMBC (H ⌒ C) correlations of **1** and **2**

α,β-unsaturated lactone ring and a seven-membered α,β-unsaturated lactone ring (Fig. 1).

A six-membered α,β-unsaturated lactone ring was assigned to the side chain of **1** due to the presence of a EI mass spectral fragment ($m/z = 111$) and the results of ^{1}H–^{1}H COSY and HMBC experiments (Liu and Huang 1984; Chen et al. 1999). In the ^{1}H–^{1}H COSY spectrum, H-20 (δ_H 1.99) was correlated with Me-21 (δ_H 0.94, d, $J = 6.3$ Hz) and H-22 (δ_H 4.43) while CH_2-23 (δ_H 2.08, 2.34) was correlated with H-22 and H-24 (δ_H 6.59, d, $J = 6.5$ Hz). In the HMBC spectrum (Fig. 2), the Me-27 (δ_H 1.87) protons were correlated with C-24 (δ_C 139.5), C-25 (δ_C 128.1) and C-26 (δ_C 166.6). The HMBC correlations of Me-21 protons were correlated with C-17 (δ_C 47.2), C-20 (δ_C 39.1) and C-22 (δ_C 80.4) indicated the connection of the six-membered, α,β-unsaturated lactone ring with the C-20 (Fig. 2). In addition, the characteristic proton signals of H-1 (δ_H 6.12, d, $J = 12.6$ Hz) and H-2 (δ_H 5.92, d, $J = 12.6$ Hz), and the HMBC correlations of H-1 with C-5 (δ_C 44.4) and C-9 (δ_C 29.0), H-2 with C-3 (δ_C 167.2) and C-10 (δ_C 33.5), Me-29 (δ_H 1.34) and Me-30 (δ_H 1.35) with C-4 (δ_C 84.2) and C-5 showed the presence of a seven-membered, unsaturated lactone ring which was assigned as ring A.

The main difference observed between compound **1** and kadsulactone A (Chen et al. 1990) was the hydroxyl group located at C-6 (δ_C 65.8) in kadsulactone A was changed to connect at C-7 (δ_C 68.5) in **1**, and that was further

confirmed from the ^{1}H–^{1}H COSY correlations between H-7 (δ_H 3.66) with CH_2-6 (δ_H 0.96, 2.04) and H-8 (δ_H 1.95, d, $J = 6.0$ Hz) and the HMBC correlation of H-7 with C-5, C-6 (δ_C 33.2), C-8 (δ_C 51.2), C-9 (δ_C 29.0) and C-14 (δ_C 48.3).

The CD spectrum of **1** showed a negative Cotton effect at 238 nm ($\Delta\varepsilon = -7.6$), indicating that **1** had the *S*-configuration at C-22 (Chen et al. 1990, 1999). NOESY correlations (Fig. 3) of Me-18 (δ_H 0.96) with H-20, Me-30 with H-5 (δ_H 2.45, dd, $J = 13.9, 4.3$ Hz), and H-7 with H-5 and Me-28 indicated that H-5, H-7, H-17, Me-28 and Me-30 were α-oriented, and H-8 and Me-18 were β-oriented. These were also confirmed by single-crystal X-ray analysis of **1** (Fig. 4).

Schisphendilactone B (**2**) was isolated as an amorphous powder, and gave a molecular formula of $C_{30}H_{38}O_6$, as determined by HRESIMS (*m/z* 493.2588 ($[M + Na]^+$, calcd 493.2590)), requiring eleven degrees of unsaturation.

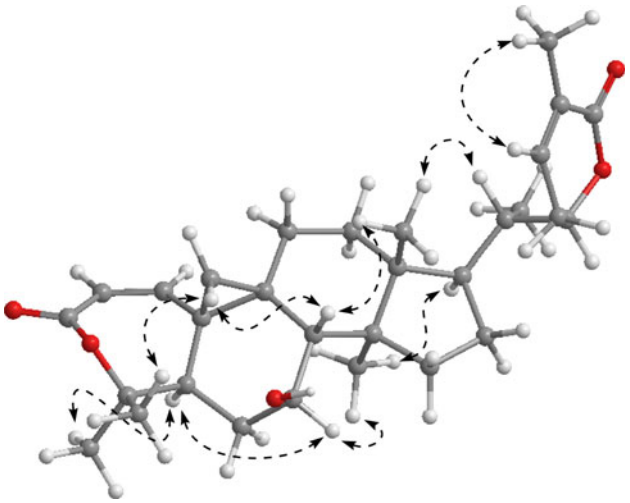

Fig. 3 Selected ROESY: H ↙ ↘ H correlations of **1**

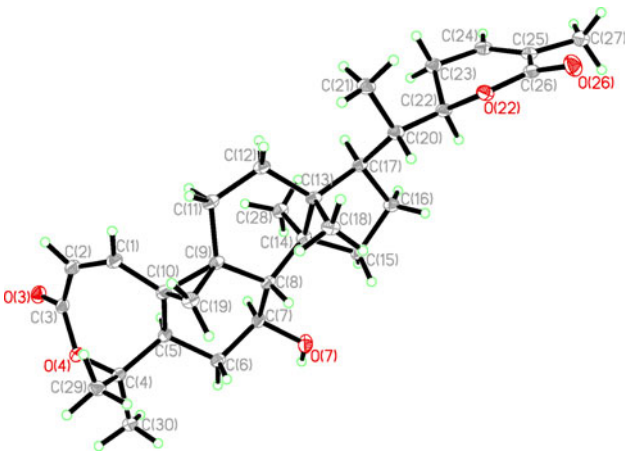

Fig. 4 X-ray crystal structure of **1**

The IR absorptions of **2** indicated the presence of hydroxyl (3,434 cm^{-1}) and lactone (1,721 and 1,662 cm^{-1}) functional groups. Analysis of the ^{1}H, ^{13}C NMR and DEPT data revealed the occurrence of six methyls (one secondary methyl and five tertiary methyls), six methylenes, nine methines (two oxygenated and four olefinic), and nine quaternary carbons (two carbonyls, three oxygenated and three olefinic). Analysis of the NMR spectroscopic data of **2** showed this compound are structural similar to lancilactone A (Chen et al. 1999).

Detailed comparison of ^{1}H and ^{13}C NMR data of **2** with those of lancilactone A showed that the differences were the appearance of a trisubstituted epoxide (δ_C 58.1 and 58.4; δ_H 3.70) (Lei et al. 2004, 2007), and a carbonyl (δ_C 197.5) in **2** and the disappearance of a double bond C-10 and C-19 (δ_C 137.9 and 144.2; δ_H 6.42) and a oxymethine group (δ_C 84.2; δ_H 5.02) in lancilactone A. The HMBC (Fig. 2) correlations of H-2 (δ_H 6.22, d, $J = 12.5$ Hz) and H-5 (δ_H 1.61) with C-10 (δ_C 58.1), of H-1 (δ_H 5.73, d, $J = 12.5$ Hz) with C-19 (δ_C 58.4), and of H-19 (δ_H 3.70) with C-1 (δ_C 142.8), C-8 (δ_C 165.4), C-9 (δ_C 128.6), C-10 (δ_C 58.1), and C-11 (δ_C 197.5), verified that the epoxide group was located between C-10 and C-19. This assignment was in accord with the observed downfield chemical shifts for the C-1 and C-2 signals from δ_C (144.6 and 117.6) in lancilactone A to δ_C (142.8 and 127.5) in **2**, respectively. In addition, the HMBC (Fig. 2) correlations of both Me-18 (δ_H 0.94) with C-11 and H-19 (δ_H 3.70) with a carbonyl group (δ_C 197.5) assigned the carbonyl group to be C-11.

The stereochemistry of compound **2** was established by careful analysis of the CD and ROESY spectrum. The CD spectrum shows a negative Cotton effect at 257 nm (−11.3), thus, C-22 (δ_C 79.8) was assigned the *S*-configuration (El Dine et al. 2008). The ROESY correlations of Me-18 (δ_H 0.94) to H-20 (δ_H 2.07) indicated that H-17 (δ_H 1.82) was α-oriented and Me-18 was β-oriented. The cross-peak between Me-30 (δ_H 1.40) with H-5 (δ_H 1.61) and Me-28 (δ_H 1.12), indicated the α-orientation of Me-30, H-5 and Me-28. In addition, H-19 showed correlations with H-1 (δ_H 5.73) and H-7β (δ_H 2.52) indicating the epoxy ring was α-orientated. Consequently, the structure of compound **2** was elucidated as shown.

All the compounds were evaluated for their in vitro growth inhibitory effects against five human cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW-480) using a previously described method (Monks et al. 1991). The results are summarized in Table 2. Compound **2** showed significant cytotoxicity against the SW480 cell line with an IC_{50} value of 8.81 μM and showed cytotoxic effects on the other tested cells with IC_{50} values range between 11.75 and 18.56 μM.

In addition, all the compounds were also tested for their potencies in preventing the cytopathic effects of HIV-1 in

Table 2 IC_{50} values (μM) of triterpenoids from *S. sphenanthera* for human tumor cell lines

Compound	HL-60	SMMC-7721	A-549	MCF-7	SW480
1	>40	>40	>40	>40	>40
2	18.56	11.75	11.90	12.70	8.81
3	>40	>40	>40	>40	>40
4	>40	>40	>40	>40	>40
5	>40	>40	>40	>40	>40
DDP[a]	1.69	9.58	14.09	16.80	15.10
Paclitaxel[a]	<0.008	<0.008	<0.008	<0.008	<0.008

[a] DDP (cisplatin) and paclitaxel were used as positive controls

Table 3 Summary of cytotoxicities and Anti-HIV-1 Activities

Compound	Cytotoxicity (CC_{50}) (μg ml^{-1})[a]	Anti-HIV activity (EC_{50}) (μg ml^{-1})	TI (CC_{50}/EC_{50})
1	47.61	8.79	5.42
2	8.77	1.09	8.05
3	58.93	28.97	2.03
4	49.19	8.23	5.98
5	60.90	0.52	117.12
AZT	1,252.34	0.00534	234,520.60

TI therapeutic index

[a]Minimal cytotoxicity against C8166 cells when $CC_{50} > 100$ μg ml^{-1}

C8166 and for cytotoxicity measured in parallel with the determination of antiviral activity, by using AZT (*=3′-azido-3′-deoxythymidine*) as a positive control ($EC_{50} = 0.00534$ μg ml^{-1} and $CC_{50} = 1252.34$ μg ml^{-1}). Compound **5** exhibited promising anti-HIV-1 activity with an EC_{50} value of 0.52 μg ml^{-1} (TI = 117.12). Other compounds (**1–4**) showed weak anti-HIV-1 activities with EC_{50} in the range 0.52–28.97 μg ml^{-1} (Table 3).

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